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EXAMINER: MERTZ,P

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1812	9

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18N2/0419

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 9/5/95. ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~days~~ from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-30 are pending in the application.
   Of the above, claims 1-8 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 9-30 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Part III DETAILED ACTION

1. Applicant's election with traverse of Group II (claims 9-30) in Paper No. 8 (5 September 1995) is acknowledged. The traversal is on the ground that the restriction requirement is improper because the claims of Group I and Group II are closely related in inventive concept. This is not found persuasive because the *in vitro* and *in vivo* methods of Groups I and II respectively, require separate searches, since the inventions are distinct. The Groups as delineated in the restriction requirement are patentably distinct one from the other such that each invention could, by itself, in principle, support its own separate patent (as shown by the arguments put forth in the written restriction requirement). Furthermore, the search and examination of each of the methods would be unduly burdensome on the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

2. The disclosure is objected to because of the following informalities:

A statement as required by 37 C.F.R. §1.821(f), that states that the content of the "Sequence Listing" in paper form and the computer readable form of the "Sequence Listing" are the same and, as required by 37 C.F.R. §1.821(g), also states that the submission

includes no new matter, is not included in the application. Appropriate correction is required.

3. Claims 9-30 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a method for stimulating erythropoiesis with thrombopoietin having the sequence shown in SEQ ID NO:2 or with thrombopoietin and erythropoietin, the thrombopoietin having the sequence shown in SEQ ID NO:2. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Claims 9-13, 15-22 and 25-30, broadly encompasses the use of any "TPO" from any species. However, the specification only enables a human thrombopoietin (TPO) of amino acid sequence shown in SEQ ID NO:2, the polypeptide having specific characteristics. These properties may differ structurally, chemically and physically from other known growth factors. Moreover, it is well-known that the name of a protein is subject to change and often refers to more than one product (tpo also refers to thyroid peroxidase). The claims do not identify the protein composition by any structural information. Therefore, it would require undue experimentation for the skilled artisan to determine all the other proteins named by the acronym "TPO" that would possess the desired activity i.e. stimulate erythropoiesis (the acronym for thymopoietin is also TPO). One of ordinary skill in the art could not practice the invention because of the quantity of experimentation required in

determining the other TPO peptides, as recited in the claims. To avoid confusion over patentably distinct proteins with the same name or similar discrete properties, it is suggested that the claims be amended to recite the enabled peptide by including amino acid sequence by SEQ ID NO., molecular weight, and/or other functional properties that are disclosed in the specification.

Claims 15 and 25 recite "a method wherein the TPO comprises a sequence of amino acids selected from the group consisting of ..... in SEQ ID NO:2.....", which also reads on "a fragment of SEQ ID NO:2". The specification mentions the different peptide fragments of TPO that may be utilized in the invention (see page 5, lines 30-36; and page 6, lines 1-17), but is non-enabled for such because it is not predictable if a fragment of TPO would have similar activity as the full-length TPO peptide because fragmentation is expected to abolish activity. Absent structure/function studies it would require undue experimentation on the part of the skilled artisan to obtain the various fragments that would possess the desired activity. No fragment of any kind of the mature TPO peptide has been demonstrated to have activity; therefore the aforementioned terms should not be used to describe other molecules that may have TPO peptide activity. The specification does not disclose which amino acids may be essential for activity. Without such guidance, the skilled artisan would have to obtain fragments by random amino acid alterations; however, randomly substituting or deleting

residues from a protein is expected to inactivate the protein. The disclosure does not provide any working example of a peptide shorter than the entire SEQ ID NO:2, therefore, in the absence of sufficient examples and absent guidance it would require undue experimentation on the part of the skilled artisan to obtain fragments of the amino acid sequence of SEQ ID NO:2 which possess the desired and favorable characteristic of the TPO peptide, and further in the absence of sufficient information to predict the results with an adequate degree of certainty (Ex Parte Forman, 230 USPQ 546).

With respect to claims 28-30 which recite "..in an amount sufficient for increasing reticulocyte counts at least 2-fold over baseline reticulocyte counts", the specification is non-enabling for the scope of such. On pages 36-38 applicants have disclosed that the baseline reticulocyte counts of anemic animals (mice treated with radiation and a chemotherapeutic drug), which were administered TPO showed increased erythropoietic recovery when compared to anemic animals which were administered buffer. However, Figure 2 indicates that the level of red blood cells in anemic animals which were administered TPO increased to that of baseline reticulocyte counts as is evident form the graph. From Figure 2, it appears that in the Group 1 mice (animals treated with radiation, a chemotherapeutic drug and buffer) the RBC counts did not return to baseline levels, while in the Group 2 mice (animals

treated with radiation, a chemotherapeutic drug and 25 kU/day TPO) and in the Group 3 mice (animals treated with radiation, a chemotherapeutic drug and 75 kU/day TPO) the RBC levels returned to baseline levels (i.e. returned to levels prior to radiation and treatment with the chemotherapeutic drug) but not 2-fold over baseline levels as recited in the claims. Therefore, since it would be that applicants intend to treat anemic mammals (i.e. mammals with a decreased baseline RBC count), it is suggested that these claims be amended to encompass what is enabled in the specification.

In view of the above discussion, the claims are not commensurate in scope with the specification but are directed to products that are broader than the supporting disclosure.

4. Claims 9 and 18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is confusing for failing to identify what the acronym TPO indicates, since in first occurrence the full meaning of acronyms should be denoted for clarification.

Claim 18 is confusing for failing to identify what the acronym EPO indicates, since in first occurrence the full meaning of acronyms should be denoted for clarification.

5. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 9-30 are rejected under 35 U.S.C. § 103 as being unpatentable over Evatt et al. (1976) and McDonald et al. (1989).

Evatt et al. teaches the administering of partially purified human erythropoietin (EPO)and thrombopoietin (TPO) to mice, and also discloses that currently available partially purified preparations of erythropoietin and thrombopoietin may be capable of stimulating both platelet and red cell production if used in sufficient quantities (pg. 547, see abstract, especially column 2, last 6 lines; pg. 557, lines 7-9).

McDonald et al. teach a four-step procedure for the purification of TPO, in which a homogeneous product was obtained as judged by SDS-PAGE and chromatofocusing, the purified product

suitable for further studies including amino acid sequencing to lead to cloning of its gene and production of the recombinant product (pg. 865, see abstract; pg. 866, see Table 1; pg. 869, column 2, Figures 8-9; and pg. 870, column 2, last para).

Given the success of each of the above references, it would have been obvious to one of ordinary skill in the art to devise a method for stimulating erythropoiesis, or a method for stimulating erythropoiesis and thrombopoiesis, comprising administering purified TPO (as obtained by McDonald et al.) or a combination of EPO and TPO because Evatt et al. teach the administration of the hormones TPO and EPO, and also disclose that the administration of the purified hormones may be capable of stimulating both erythropoiesis and thrombopoiesis. The ability of EPO to stimulate erythropoiesis is well-known, the ability of TPO to stimulate thrombopoiesis is well-known and also reiterated by Evatt et al. (pg. 547, first para, lines 1-6). The teachings of Evatt also suggest that purified TPO can be used to stimulate erythropoiesis and purified EPO can be used to stimulate thrombopoiesis, if used in sufficient quantities. Therefore, one would have been motivated to use the hormones together, to increase the clinical efficacy of the invention and to obtain the known functions and advantages of stimulating both erythropoiesis and thrombopoiesis with the hormones TPO and EPO (as per the teachings of Evatt et al.).

With respect to claims 10-13 and 19-22, since the administration of the hormones EPO and TPO would be to a person in need thereof, i.e. it would be obvious to one of ordinary skill in the art that the desired effects of the hormones would be to obtain normal RBC counts. Therefore, the limitations in the claims, are standard clinical manifestations indicative of anemia which is a normal side-effect of chemotherapy and radiation therapy, and it would be obvious to one of ordinary skill in the art that it would be desirable to increase the levels of RBC's. With respect to claims 16-17 and 26-27, it would be routine to one of ordinary skill in the art to determine the dose of the hormone and the appropriate concentration which is the optimum, most effective and would result in the maximum effect desirable.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use a combination of TPO with an erythropoietic agent such as EPO to increase the clinical efficacy of the claimed invention (i.e. a method of stimulating erythropoiesis) since the combination could be synergistic. To combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose would have been obvious to one of ordinary skill in the art at the time the invention was made. The combination would have

been obvious to the skilled artisan and the results achieved would have been expected (In re Kerkhoven, 205 USPQ 1069).

No claims are allowed.

6. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Prema Mertz whose telephone number is (703) 308-4229. The Examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Garnette D. Draper, can be reached on (703) 308-4232.

Papers related to this application may be submitted to Group 1800 in Crystal Mall 1 by facsimile transmission, in conformity with the notice published in the official Gazette, 1096 0G 30 (November 15, 1989). The FAX phone number for Art Unit 1812 is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Prema Mertz Ph.D. PM
Examiner
April 11, 1996

GARNETTE D. DRAPER
SUPERVISORY PRIMARY EXAMINER
GROUP 1800